*Research Letter*

# Impact of FDA Regulatory Approach on the 0/2h-Algorithm for Rapid Triage of Suspected Myocardial Infarction

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**Brief summary:** The 0/2-hour-algorithm using hs-cTnT as approved by the FDA provides very high safety and efficacy for patients with suspected AMI.

Serial cardiac troponin (cTn) measurements complement clinical assessment and the electrocardiogram in the early diagnosis of acute myocardial infarction (AMI). The 5$^{th}$ generation cTnT assay (high-sensitivity cardiac troponin (hs-cTnT)) has been approved by the Food and Drug Administration (FDA) in January 2017 as the first clinically available, more sensitive cTn-assay within the United States.(1)

The FDA-approved use of hs-cTnT differs in two important details from the contemporary use of hs-cTnT in most other countries. First, very low concentrations are only reported down to the limit of quantification (LoQ; 6ng/L) as compared to the limit of detection (LoD; 3ng/L). Second, the FDA required the determination of the 99$^{th}$-percentile upper-reference limit (URL) in an age-matched population to that of patients presenting to the emergency department (ED) with suspected AMI, whereas the 99$^{th}$-percentile URL for use outside the United States was determined in healthy and often younger individuals. As a consequence, the FDA-approved 99$^{th}$-percentile URL (19ng/L) is slightly higher as compared to the 99$^{th}$-percentile used outside the United States (14ng/L).(2) Among several well-validated rapid triage algorithms taking advantage of the higher sensitivity and higher accuracy provided by hs-cTn, the 0/2-hour-algorithm seems to particularly well combine safety and efficacy.(3) The performance of the 0/2-hour-algorithm, which integrates the hs-cTnT concentrations at ED presentation and at 2h together with the absolute changes within the first 2h, is unknown in the FDA-approved setting.

We therefore prospectively assessed the safety and efficacy of the 0/2-hour-algorithm using hs-cTnT as approved by the FDA in a large diagnostic multicentre study enrolling unselected patients presenting with symptoms suggestive of AMI to the ED of twelve hospitals in five European countries (Switzerland, Spain, Italy, Czech Republic, Poland; clinical trial registration: NCT00470587). The study complies to the principles of the Declaration of Helsinki and was approved by the local ethic committee. All patients provided written informed consent. Patients presenting with ST-Segment-Elevation MI were excluded. The final diagnosis was centrally adjudicated by two independent cardiologists based on all available clinical

information including cardiac imaging and serial measurements of hs-cTnT. All patients underwent a clinical assessment that included medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood test, and chest radiography. Concentrations of (hs-)cTn were measured at presentation and serially thereafter as long as clinically indicated using different local (hs)-cTn assays in clinical use at the participating institutions. Treatment of patients was left to discretion of the attending physician. Safety of rule-out was quantified by the negative predictive value (NPV) and sensitivity for AMI, accuracy of rule-in by the positive predictive value (PPV) and specificity, and efficacy by the proportion of patients assigned to rule-out/rule-in based on the 0- and 2-hour blood-samples. The 0/2-hour-algorithm was applied twice using A) the FDA-approved approach and B) the original 0/2-hour-algorithm as used outside the United States (Figure 1). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Among 2703 patients included in this analysis, AMI was the final diagnosis in 384 (14.2%) patients and 392 (14.5%) patients assessed by the FDA-approved 99$^{th}$ percentile URL and the original 99$^{th}$ percentile URL, respectively. Safety of rule-out by the FDA-approved approach was very high with a NPV of 99.8% (95%Cl 99.5-100%) and a sensitivity of 99.2% (95%Cl 97.7-99.8%). In patients triaged towards rule-in, PPV was 77.0% (95%Cl 72.4-81.1%) and specificity 96.2% (95%Cl 95.4-97.0%). Efficacy was very high with 79.2% of patients being triaged towards either rule-out or rule-in. Overall, the performance using the FDA-approved approach was highly comparable to that of the original (Figure). In patients with renal dysfunction (RD), defined as estimated glomerular filtration rate <60ml/min/1.73m$^2$ (n=383, 14.2%) using the FDA-approved approach, safety of rule-out was comparable to patients with normal renal function (NPV 100% versus 99.8%, p=0.99) while accuracy of rule-in (PPV 72.4% versus 78.9%, p=0.004) and overall efficacy (49.1% versus 83.8%, p<0.001) were significantly reduced in patients with RD. Similar to the main findings, no difference in safety

of rule-out, accuracy of rule-in or overall efficacy was observed between the FDA-approved approach and the original 0/2h algorithm.

Our findings suggest that the 0/2-hour-algorithm using hs-cTnT as approved by the FDA provides very high safety and efficacy for the triage towards rapid rule-out or rule-in of AMI.

Data available on request from the authors

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**Figure 1:** Diagnostic performance of the 0/2-hour-algorithm modified according to the FDA regulations for rapid rule-out and rule-in of non-ST-segment-elevation myocardial infarction (NSTEMI)

FDA = Food and Drug Administration; NSTEMI = Non-ST-segment-elevation myocardial infarction; hs-cTnT = high-sensitivity cardiac troponin T; NPV = negative predictive value; PPV = positive predictive value